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Contradictory Results with High-Dosage Rifamycin in Mice and Humans

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Using the standard model of treatment for murine tuberculosis, daily rifapentine (RPT) was 4 times more potent than rifampin (RIF) in sterilizing the organs (1), whereas Tuberculosis Trials Consortium (TBTC) study 29 failed to find any increase in sterilizing activity when RPT was given daily (2). The authors suggest that the contradiction was due to food being given to the mice but not to patients at dosing or to protein binding having different effects in murine and human lesions or to the dichotomous endpoint used. These explanations, while reasonable, do not seem adequate to explain the contradiction found between the large effect of moving from once weekly to daily dosing with RPT in the mouse model and the apparent complete absence of a similar effect in patients.

We have provided an explanation for the discrepancy based on the results in several early clinical trials with isoniazid (INH) alone where patients were categorized as slow or rapid acetylators with consequent widely different exposures to INH (3). In these trials, efficacy was significantly ($P = 0.006$) related to the peak INH concentrations but not at all to the area under the dose-response curve (AUC)/MIC ratio. It seemed that over the year of treatment, successive high peaks gradually killed INH-resistant mutants with low MICs. By analogy, the same process might occur during long-term treatment with rifamycins, with the place of INH-resistant mutants with low MICs being taken by persisters with low degrees of RIF tolerance (4).

RIF-tolerant persisters have been shown to occur frequently in the sputum samples from patients (5), but the only evidence for their appearance in murine tuberculosis is the finding, 10 months after infection, of strains that grew much better in liquid medium than on solid medium (6). The standard mouse model starts treatment soon after infection, too soon for persister populations to appear. Under these circumstances, efficacy would be related to the AUC/MIC ratio as has been amply demonstrated by the AstraZenica group in an acute murine model (7). However, as persisters are present in sputum samples from patients, their response to long-term treatment is likely to be related to peak concentrations. The move from weekly dosage with RPT to daily dosage greatly increases the AUC with consequently increased sterilizing activity in the mouse, but the peak concentrations are little altered, with consequent failure to increase efficacy in humans.

It may be argued that this explanation relies on much guesswork. What is needed is evidence. We need to know how long it takes for persister populations to appear in chronic murine tuberculosis. We are not helped by the recent work of Rosenthal and colleagues (8) in which they prolonged the period between infection and the start of treatment without a demonstration of the emergence of rifamycin tolerance. This period may have been too short. When we know when tolerance emerges, a repeat study comparing RPT and RIF would be needed to justify our explanation. Such a study is urgently required to avoid further wasted research.

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